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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/597,286	10/20/2006	Jose Vicente Castell Ripoll	020884-000009	8850

24239 7590 09/01/2009

MOORE & VAN ALLEN PLLC
P.O. BOX 13706
Research Triangle Park, NC 27709

EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

MAIL DATE	DELIVERY MODE
09/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/597,286	RIPOLL ET AL.	
	Examiner	Art Unit	
	CELINE X. QIAN	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11 and 13-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11 and 13-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 July 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1106*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-9, 11, 13-20 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group II in the reply filed on 7/22/09 is acknowledged. The traversal is on the ground(s) that the special technical feature of Groups I-IV makes a contribution over cited prior art, Brimer in view of Gomez-Lechon et al. This is not found persuasive, and the restriction requirement has been withdrawn.

Accordingly, claims 1-9, 11, 13-20 are currently under examination.

Claim Objections

Claims 2-8, 14-20 are objected to because of the following informalities: Claims 2-8 recite "method according to claim 1," it is suggested to change to "The method according to claim 1" to improve grammar. Similarly, claims 14-20 referring to the cell model of claim 9 should recite "The human cell model of claim 9, wherein..." Claim 20 recites "cells comprises..." which should be changed to "cells comprise" or "cell comprises" to improve grammar. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 13 is rejected under 35 U.S.C. 102(b) as being anticipated by Brimer et al (see IDS).

The claim is drawn to a method to confer any cell line the capacity to metabolize xenobiotics in a controlled manner, wherein the method comprises the step of transfecting the cell line with more than one adenoviral vectors that expresses Phase I enzymes, Phase II enzymes or cytochrome p450 reductase.

Brimer et al. disclose transfecting Caco and LLC-PK1 cells with adenoviral vector expressing CYP3A4 and NADPH P450 reductase (see abstract and Table 1), which is a Phase I enzyme and a cytochrome p450 reductase. Therefore, Brimer et al. disclose the instantly claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9, 11, 13-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bort et al (IDS), in view of Gomez-Lechon et al (IDS).

Gomez-Lechon et al. teach that *in vitro* metabolism models can speed up the identification of new drug candidates, and pharmaceutical companies are increasingly making use of such model. Gomez-Lechon et al. discuss advantages and limitation of currently existing *in vitro* models including liver microsomes, human heptocytes and CYP engineered cells (see Table 1). Gomez-Lechon et al. teach that using human hepatocytes for this application has limitations such as losing expression of many hepatic proteins including CYPs during culture (see page 297, 1st col., 2nd paragraph). Gomez-Lechon et al. also teach that using hepatic cell lines expressing single CYP has limitations including lack of phase II enzymes, uncoupled metabolic pathways, no physiological levels of enzymes, impossibility of induction studies and no in *vitro/in vivo* correlations (see Table 1). Moreover, in cDNA-expressing systems a single CYP interacts with an electron-carrier/supplier protein, while in liver hepatocytes many CYPs can interact with them, thus lead to incorrect predictions of the relative distributions of individual CYPs to the metabolism of a drug (see page 299, 1st col., last paragraph). Gomez-Lechon et al. further indicate that the future improvements for those CYP engineered cells to serve as *in vitro* model includes co-expression of several CYPs, expression of phase II enzymes and development of cells responsive to induction (see Table I). Gomez-Lechon et al. state that there is a need for hepatic cell lines expressing the whole spectrum of human xenobiotic-metabolizing enzymes as an alternative to primary cultures, and the hepatic-specific expression of a given gene is accomplished by the concerted action of a number of liver-enriched and ubiquitous regulatory factors. Gomez-Lechon et al. suggest that a promising experimental approach is the use of adenoviral vectors to allow simultaneous expression of multiple genes (see page 307, bridging paragraph). Gomez-Lechon et al. teach that adenoviruses encoding two of the most relevant

liver enriched transcription vectors have been successfully generated and transduced to HepG2, a cell line of hepatic origin.

However, Gomez-Lechon et al. do not teach actual practice of the suggested approach of transfecting multiple adenoviral vector that expresses different phase I or phase II enzyme to cells of hepatic origin.

Bort et al. teach a method of studying hepatic metabolism of diclofenac using liver epithelial cell lines that transfected with specific CYP genes (see page 792, last paragraph through page 793, 1st col.). Bort et al. teach that comparison of metabolism of diclofenac in both primary hepatocytes and said genetically engineered cell lines is able to identify CYP that are required for said drug metabolism (see page 793, last paragraph and Figure 7).

It would have been obvious an ordinary skill in the art to introduce adenoviral expression vectors that expresses different Phase I or Phase II enzymes to cells of hepatic origin to build an *in vitro* model for studying drug metabolism based on the teaching of Gomez-Lechon et al. The teaching of Gomez-Lechon et al. clearly established that there is a need for such engineered cell line to be made for the purpose of studying drug metabolism. Bort et al. has demonstrated that this approach is feasible using hepatic cell lines transfected vector expressing single CYP enzymes and assessing hepatic metabolism of diclofenac. Since Gomez-Lechon et al. taught the limitation of cell line expressing single CYP, an ordinary skilled in the art would have been motivated to modify such system by introducing additional Phase I or Phase II enzymes such that the cell line will reflect the whole spectrum of human xenobiotic metabolizing enzyme expression profile. The level of skill in the art is high as evidenced by transducing hepatic cell lines using adenoviral vectors have been proven successful, and the identification of cDNA

encoding Phase I and Phase II enzymes wherein such information is available to the public. The ordinary artisan having the knowledge of cDNA encoding of Phase I and Phase II enzymes would have reasonable expectation of success to generate adenoviral vectors expressing sense or anti-sense drug metabolizing enzymes to up or down-regulating specific enzymes in a cell of hepatic origin to best mimic the hepatocytes *in vivo*. Once such *in vitro* model is made, it would have been obvious to the ordinary artisan to use such model to study metabolism, pharmacokinetics, potential idiosyncratic heptotoxicity and or potential medicament interaction of a drug as claimed. The claimed cells expressing different phase I or phase II enzymes and the method of making them by transfecting cells with adenoviral expression vectors would have been obvious because a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp, in the instant case, as suggested by Gomez-Lechnon et al., to make the claimed cell model. As stated above, the ordinary artisan having the knowledge of cDNA encoding of Phase I and Phase II enzymes would have reasonable expectation of success to generate adenoviral vectors expressing sense or anti-sense drug metabolizing enzymes to up or down-regulating specific enzymes in a cell of hepatic origin. Therefore, the claimed invention is not of innovation but of ordinary skill and common sense, and would have been *prima facie* obvious to the ordinary artisan at the time the invention was made.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 1, the recitation of "to obtain expression vector cells transitorily express said ectopic DNA sequences and present a different phenotypic profile of Phase I or Phase II drug biotransformation enzymes" renders the claim indefinite because it is unclear how the expression vector and/or cells are obtained in the context of the claim. Moreover, it is unclear what phenotypic profile is presented in the model, and what the profile is different from. In other words, different means one is not the same from the other. The claim language is not clear cells with adenoviral vector encoding drug enzymes are different from a control cell line, another cell model? The recitation of "a singular cell model…wherein said model comprises a set of recombinant vectors...building a singular cell model capable of reproducing in vitro the metabolic idiosyncrasy of humans from said cells transformed..." also renders the claim indefinite because it is unclear whether said cell model comprises a set of vector, a single cell, or multiple cells. The overall language is confusing whether the term singular is referring to the number of cells or a cell model. If it is referring to a cell model, it is unclear how this term is defined relative to a cell model as claimed. Does it mean one type of cell, or a clone of a type of cell, or cells transformed with same expression vector? The metes and bounds of the claim cannot be established in view of the ambiguous claim language. Claims 2-8 are rejected because they depend on claim 1

Regarding claim 13, the recitation of "a set of more than one adenoviral vectors selected from the group consisting of Phase I enzymes, Phase II enzymes, and cytochrome P450

reductase" renders the claim indefinite because none of the enzyme from the group is an adenoviral vector.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELINE X. QIAN whose telephone number is (571)272-0777. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Celine X Qian /
Primary Examiner, Art Unit 1636